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Applicant(s):	Chaudry	
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Art Unit:	1616	
Examiner:	James Henry Alstraum Acevedo	
Title:	FORMULATIONS AND METHODS FOR TREATING RHINOSINUSITIS	

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APPEAL BRIEF UNDER 37 CFR § 41.37

This Appeal Brief supplements the Appeal Brief filed on May 6, 2011 and is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed January 6, 2011 and further in view of the "Notification of Non-Compliant Appeal Brief" dated May 10, 2011.

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1. ***Real Party in Interest.***

The real party in interest in this appeal is Dey L.P., the assignee of the above-referenced patent application.

2. ***Related Appeals and Interferences.***

A Notice of Appeal has been filed in Application No. 10/414,682, assigned to Dey, L.P. On May 2, 2011, an Appeal Brief was filed in the '682 application. The present application is a continuation-in-part of the '682 application and Application No. 10/414,756 (now U.S. Patent No. 7,811,606). The legal representative for the appellant in the '682 application is the same as in the present application. There are currently no decisions rendered by the Board in the '682 application. As a final matter, there are no related interferences involving this application or its subject matter.

3. ***Status of Claims.***

Claims 2-3, 7-9, 13-21, 26, 31-34, and 36-70 have been canceled. Claims 1, 4-6, 10-12, 22-25, 27-30, 35, 71-77 are pending in the application and all stand rejected as unpatentable over a combination of prior art references as set forth in greater detail below. All rejections of record are appealed herein. Accordingly, claims 1, 4-6, 10-12, 22-25, 27-30, 35, 71-77, which were finally rejected in the Office Action of August 6, 2010, are the subject of this appeal.

4. ***Status of Amendments.***

All claim amendments presented during prosecution were entered and are set forth in the clean copy of the pending claims appended to the brief. No claim amendments have been filed subsequent to final rejection dated August 6, 2010.

5. ***Summary of Claimed Subject Matter.***

The currently claimed invention comprises a nasal pharmaceutical formulation for the treatment of rhinitis comprising an aqueous suspension of 0.04% to 0.06% by weight of suspended solid fluticasone having a specific suspended solid particle size distribution profile characterized by 5 different micron ratings in combination with an antifungal agent. The recited particle size distribution has surprisingly shown to provide increased bioavailability over conventional formulations as evident by the factually reported increased magnitude of improvement in several patients (e.g., reduction in the signs and symptoms of seasonal allergic rhinitis (SAR)). That is, patients receiving the currently claimed formulations having the recited particle size distribution of fluticasone realize a surprisingly increased reduction in the symptoms of SAR.

As discussed more detail below, formulations including the currently claimed formulations were compared to Flonase. The recited particle size distribution of the currently claimed formulations was the only difference from the Flonase formulation. Surprisingly, the recited particle size distribution has been shown to provide individuals with an increased reduction in the total symptoms of rhinitis as compared to the results realized by individuals receiving the same amount of active from Flonase.

Independent claims 1 recites an aqueous formulation comprising suspended particles of fluticasone in combination with an antifungal agent. See page 7, lines 7-17; page 7, line 18 through page 8, line 17; and page 11, line 13 through page 12, line 20 of the specification as originally filed. More specifically, the formulation includes an aqueous suspension of 0.04% to 0.06% by weight of suspended solid fluticasone particles having the following particle size distribution profile:

i. about 10% of the steroidal anti-inflammatory particles have a particle size of less than 0.4 microns;

ii. about 25% of the steroidal anti-inflammatory particles have a particle size of less than 0.8 microns;

iii. about 50% of the steroidal anti-inflammatory particles have a particle size of less than 1.5 microns;

iv. about 75% of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns; and

v. about 90% of the steroidal anti-inflammatory particles have a particle size of less than 5.3 microns.

See Table 1 on page 10 (end of page) of the specification as originally filed; and Table 2 on pages 16-17 (Table 2 occupies all of page 16 and the first half of page 17) of the specification as originally filed. Additionally, the present application incorporates Application No. 10/414,682 in its entirety. See page 1, lines 2-5 of the specification as originally filed. Page 13, lines 1-3 of the '682 application provides support for the recited weight percent range of fluticasone. See the response filed on February 4, 2009 amending the specification to explicitly recite this portion of the '682 application immediately prior to the paragraph beginning on page 11, line 21 of the application as originally filed. Tables 1 and 2 in the Examples section of the '682 application provide support for the recited particle size distribution. The specification of the present application was previously amended to incorporate each of these sections into the present application. See the response filed on January 6, 2011 and entered by the Examiner in the Advisory Action dated January 21, 2011 in which the entire Examples section including Tables 1 and 2 (page 22, line 13 through page 31, line 3 of the '682 application) of the '682 application was amended into the present specification after page 35, line 2 of the present application as originally filed.

Independent claim 35 also recites an aqueous formulation comprising suspended particles of fluticasone in combination with an antifungal agent. See page 7, lines 7-17; page 7, line 18 through page 8, line 17; and page 11, line 13 through page 12, line 20 of the specification as originally filed. More specifically, the formulation includes about 7.5 to about 15 mg of amphotericin β in combination with 0.04% to 0.06% by weight of suspended solid fluticasone propionate particles having the following particle size distribution profile:

i. about 10% of the steroidal anti-inflammatory particles have a particle size of less than 0.40 microns;

ii. about 25% of the steroidal anti-inflammatory particles have a particle size of less than 0.80 microns;

iii. about 50% of the steroidal anti-inflammatory particles have a particle size of less than 1.5 microns;

iv. about 75% of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns; and

v. about 90% of the steroid particles have a particle size of less than 5.3 microns.

See Table 1 on page 10 (end of page) of the specification as originally filed; and Table 2 on pages 16-17 (Table 2 occupies all of page 16 and the first half of page 17) of the specification as originally filed. Additionally, the present application incorporates Application No. 10/414,682 in its entirety. See page 1, lines 2-5 of the specification as originally filed. Page 13, lines 1-3 of the '682 application provides support for the recited weight percent range of fluticasone. See the response filed on February 4, 2009 amending the specification to explicitly recite this portion of the '682 application immediately prior to the paragraph beginning on page 11, line 21 of the application as originally filed. Tables 1 and 2 in the Examples section of the '682 application provide support for the recited particle size distribution. The specification of the present application was previously amended to incorporate each of these sections into the present application. See the response filed on January 6, 2011 and entered by the Examiner in the Advisory Action dated January 21, 2011 in which the entire Examples section including Tables 1 and 2 (page 22, line 13 through page 31, line 3 of the '682 application) of the '682 application was amended into the present specification after page 35, line 2 of the present application as originally filed.

Independent claims 75 recites an aqueous formulation comprising suspended particles of fluticasone in combination with (a) a therapeutic amount of an antiviral agent selected from the group consisting of Acyclovir, Famciclovir, Valacyclovir, edoxudine, ganciclovir, foscarnet, cidofovir (vistide), Vitrasert and Formivirsen; and (b) about 7.5 to about 15 mg of amphotericin β; and (c) about 10 to about 100 mg of doxycycline. See page 7, lines 7-17; page 7, line 18 through page 8, line 17; page 11, line 13 through page 12, line 20; and page 18, final 6 lines of the specification as originally filed. The formulation includes 0.04% to 0.06% by weight of

suspended solid fluticasone propionate particles having the following particle size distribution profile:

i. about 10% of the steroidal anti-inflammatory particles have a particle size of less than 0.4 microns;

ii. about 25% of the steroidal anti-inflammatory particles have a particle size of less than 0.8 microns;

iii. about 50% of the steroidal anti-inflammatory particles have a particle size of less than 1.5 microns;

iv. about 75% of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns; and

v. about 90% of the steroid particles have a particle size of less than 5.3 microns.

See Table 1 on page 10 (end of page) of the specification as originally filed; and Table 2 on pages 16-17 (Table 2 occupies all of page 16 and the first half of page 17) of the specification as originally filed. Additionally, the present application incorporates Application No. 10/414,682 in its entirety. See page 1, lines 2-5 of the specification as originally filed. Page 13, lines 1-3 of the '682 application provides support for the recited weight percent range of fluticasone. See the response filed on February 4, 2009 amending the specification to explicitly recite this portion of the '682 application immediately prior to the paragraph beginning on page 11, line 21 of the application as originally filed. Tables 1 and 2 in the Examples section of the '682 application provide support for the recited particle size distribution. The specification of the present application was previously amended to incorporate each of these sections into the present application. See the response filed on January 6, 2011 and entered by the Examiner in the Advisory Action dated January 21, 2011 in which the entire Examples section including Tables 1 and 2 (page 22, line 13 through page 31, line 3 of the '682 application) of the '682 application was amended into the present specification after page 35, line 2 of the present application as originally filed.

6. ***Grounds of Rejection to be Reviewed on Appeal.***

As stated in the Final Rejection dated August 6, 2010, claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE from the online Physician's Desk Reference , as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter "Flonase") in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter "Bernini"), WO 99/18971 to Harris (hereinafter "Harris"), and U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken"). Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over Flonase in view of Bernini, Harris, Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter "Doi") and U.S. Patent No. 6,608,054 to Meade (hereinafter "Meade"). Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over Flonase in view Bernini and Osbakken, and further in view of "Management of Allergic Rhiniti", Nursing Times, 2003, 99(23), Abstract to Walker (hereinafter "Walker") and "Topical Antiviral Agents for Herpes Simplex Virus Infections", Drugs Today, 1998, 34(12), Abstract to Hamuy et al. (hereinafter "Hamuy"). These are the only rejections in this appeal.

As explained more fully below, Appellant submits that the claims as grouped in the final rejection do not stand or fall together. There are several independent reasons why the claims are patentable over the cited prior art. Thus, Appellants have grouped the grounds of rejection as follows:

1) The rejection of claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, and Osbakken;

2) The rejection of claims 71-74 under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade; and

3) The rejection of claims 75-76 under 35 U.S.C. §103(a) as being obvious over any combination Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

7. ***Argument.***

The Subject Matter of the Claims is Not Obvious

Based on any Combination of Flonase, Bernini, Harris, and Osbakken

In the obviousness rejection, the Examiner asserts that Flonase teaches a nasal spray comprising an aqueous suspension of fluticasone propionate particles. However, the Examiner acknowledges that Flonase is silent regarding the recited particle size distribution. See page 11 of the final Office Action dated August 6, 2010. In an attempt to cure the deficiency of Flonase, the Examiner cites Bernini for teaching aqueous suspensions of beclomethasone having particle size distributions similar to the currently claimed fluticasone particle size distribution. The Examiner also acknowledges that Flonase fails to teach the inclusion of an antifungal agent. As such, the Examiner cites Osbakken in an attempt to cure this deficiency of Flonase. The Examiner argues that Osbakken illustrates that it was known in the art to treat rhinitis/sinusitis with formulations including an anti-inflammatory and an antifungal agent. See pages 11-12 of the final Office Action dated August 6, 2011. The Examiner concludes that it would have been obvious to a skilled artisan to (1) modify the particle size distribution of Flonase to arrive at the currently recited distribution and (2) add an antifungal agent to the Flonase formulation.

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit "no

doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases. '' *Id.* 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'' *Id* . 82 USPQ2d at 1396.

Appellants submit that the Examiner has not proven a *prima facie* case of obviousness because any combination of the cited art does not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail below.

1) Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 are not obvious over any combination of Flonase, Bernini, Harris, and Osbakken.

Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 stand rejected under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, and Osbakken;

(a) Comparison of Flonase particle size distribution with the currently claimed particle size distribution shows marked differences.

Flonase is a 50 mcg of microcrystalline aqueous suspension of fluticasone propioinate. Flonase can be used for the perennial rhinitis in patients above 12 years of age. A controlled study was performed where the fluticasone used in the Dey FP nasal spray was derived from a different source than Flonase (i.e. the Dey FP nasal spray had a different particle size distribution then Flonase). For instance, the particle size distribution of Flonase has been reported in a white paper by ChemImage (hereinafter "ChemImage") to be significantly different than the distribution recited in the currently claimed invention. A copy of ChemImage is attached to this Appeal Brief. Figure 1 of ChemImage shows the Raman dispersive spectra of Flonase and Figure 3 lists the particle size of Flonase (i.e., innovator) as follows: (i) D10 = 1.0 microns; (ii)

D50 = 4.7 microns; and (iii) D90 = 13.5 microns. That is, ChemImage shows that the particle size distribution of Flonase has the following distribution:

Flonase PSD as reported by ChemImage

D10	D50	D90
1.0	4.7	13.5

For comparison, the currently claimed invention recites, the following particle size distribution:

Claimed PSD

D10	D50	D90
0.4	1.5	5.3

Upon comparison of the reported particle size distribution of Flonase with the currently claimed distributions, it is readily apparent that the particle size distribution of Flonase generally contains larger particles and a wider distribution of particles. For instance, about 50% of the particles in Flonase are greater than 4.7 microns. To the contrary, the currently claimed invention recites that about 90% of the fluticasone particles are less than 5.3 microns. Furthermore, the reported D50 level for Flonase is roughly 3 times larger than that of the currently claimed distribution (i.e., 4.7 microns as compared to the currently recited 1.5 micron rating). Accordingly, the Flonase particle size distribution is quite different than the currently claimed particle size distribution in several respects.

Additionally, one skilled in the art would have no rational basis for modifying Flonase to have the particular particle size distribution recited in each of the currently pending independent claims. **Such a modification would require a substantial alteration of the Flonase particle size distribution, particularly considering the lack of any teaching in the art to make such a modification.** Additionally, Appellants note that the mere possibility that the Flonase particle size distribution could be modified in such a way does not mean that such a modification would have been obvious to the skilled artisan, particularly in view of no teaching in the art that such a modification would provide the surprising results discussed below.

(b) The currently claimed particle size distributions provide surprising results.

Appellants note that the Example 6 of the present specification and Figs. 1-4 (all of which has been amended into the present application from a parent application as discussed above in the response filed on January 6, 2011 and entered by the Examiner in the Advisory Action dated January 21, 2011) provides a direct comparison between the currently claimed particle size distribution and Flonase (the only available Fluticasone product at the time of the currently claimed invention). See Example 6 of the present specification (as amended into the present specification as discussed above). As explained in Example 6, the "low dose" designation refers to the number of sprays including fluticasone received by patients. "Low dose" groups only received 1 spray of fluticasone per nostril in a day. Comparison of the Dey FP Low Dose Group with the Flonase Low Dose Group shows that the currently claimed invention provides a notable and surprising improvement from the symptoms of SAR despite both groups receiving the same amount of active. Table 1, provided below, provides an approximate quantitative value for the improved relief from the symptoms of SAR realized by patients in the Dey FP Low Dose group.

Table 1

Day	Dey FP Low Dose Group – approximate LS value	Flonase Low Dose Group – approximate LS value	% Improvement in TNSS over the Flonase Low Dose Group
2	-2.9	-2.1	**~38%**
3	-4.2	-3.3	**~27%**
4	-4.7	-3.9	**~20%**
5	-5.2	-4.7	**~11%**
6	-5.3	-4.4	**~20%**
7	-5.9	-4.5	**~31%**
8	-5.8	-5.1	**~14%**
9	-6.3	-5.8	**~9%**
10	-6.8	-6.2	**~10%**
11	-7.4	-5.6	**~21%**
12	-7.4	-6.1	**~19%**
13	-7.4	-6.2	**~19%**
14	-7.8	-6.5	**~20%**

Appellant submits that one skilled in the art (and one suffering from the symptoms of seasonal allergic rhinitis) would recognize the aforementioned percentages of TNSS improvement as not merely a minor difference of degree as suggested by the Examiner. Appellant notes that the **patients in the Dey FP Low Dose group realized these improved reductions in TNSS while receiving the same amount of fluticasone as the patients in the Flonase Low Dose group. This result is surprising because one skilled in the art would expect the same results (i.e., magnitude in relief of the symptoms) from both groups since both groups received the same amount of fluticasone. Again, the only difference in the Dey FP and Flonase formulations is the respective particle size distributions. As such, the currently claimed particle size distribution provides unexpected results.** These results provide further evidence of the non-obviousness of the currently claimed invention.

(c) Secondary references do not cure the deficiencies of Flonase or negate the surprising results realized by the currently claimed particle size distributions.

Bernini is primarily directed to a process for preparing aqueous suspensions of drug particles for inhalation into the lungs, not the nasal mucosa. Bernini's process includes the following steps: (i) preparing an aqueous solution constituting the carrier and optionally containing wetting agents, surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients; and (iv) dispersing all of the ingredients by using the same turboemulsifier. The resulting aqueous suspensions are intended for nebulisation so that the active is deposited into the lungs.

The Examiner merely cites Harris as a supporting reference to demonstrate particle sizes recognized in the art as being suitable for nasal administration and for the proposition that it is conventional to optimize particle size distributions. See page 11 of the final Office Action dated August 8, 2011. Appellants note that Harris is actually directed to mometasone formulations and does not teach or suggest the claimed fluticasone particle size distribution.

The Examiner cites Osbakken for support that it has been suggested previously to use small aerosol particles in the treatment of sinusitis and for teaching compositions including the combination of an anti-inflammatory with an antifungal agent or an antibiotic. In general, Osbakken is directed to pharmaceutical compositions including one or more active ingredients. Specifically, Osbakken is directed to compositions having a specific surface tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that "this aerosol cloud will have liquid aerosol particles" having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092].

Harris, Bernini, and Osbakken, however, fail to cure the deficiencies of Flonase discussed above, namely the currently claimed particle size distribution that provides unexpected results. Furthermore, Harris, Bernini, and Osbakken fail to provide any teaching that would provide a skilled artisan any rational basis for modifying the particle size distribution of Flonase in any manner to arrive at the currently claimed particle size distribution. For instance, the cited art is devoid of any explicit or implicit teaching that surprisingly improved reductions in the symptoms of rhinitis may be achieved by modifying the particle size distribution of Flonase, let alone to have the currently claimed particle size distribution.

Appellants note that the Examiner contends that the optimization of particle sizes distributions "is routine in the field of inhalable formulations (i.e. both oral and nasally administered) (Harris). Thus, finding the optimal particle size... is routinely practiced in th eart and as applied to the prior art, would reasonably be expected to yield the same or substantially similar particle size distribution as claimed by Applicants." See pages 14 and 17 of the final Office Action dated August 8, 2011. Moreover, the Examiner argues that "absent a showing of unexpected results, the instantly recited particle size distribution in not considered to represent non-obvious modification of the prior art, but rather merely the routine optimization of a known result effective parameter." See page 17 of the final Office Action dated August 8, 2011

The Examiner, however, has disregarded Appellants showing of criticality of the currently claimed particle size distribution. As provided in MPEP 2144.05(III), an applicant can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range. For instance, "[t]he law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). **As discussed above, the currently claimed particle size distribution does achieve unexpected results. Therefore, Appellants submit that the Examiner is in error for disregarding the showing of**

unexpected results establishing criticality of the claimed particle size distribution as mere routine optimization.

(d) Any combination of Flonase, Bernini, Harris, and Osbakken fail to render claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 as obvious.

Each of Flonase, Bernini, Harris,and Osbakken, whether considered alone or in any combination, do not teach, suggest, or render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in detail above.

2) Claims 71-74 are not obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade.

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade.

Claims 71-74 recite the addition of particular complexing agents. As such, the Examiner cites Doi for teaching suspensions for nasal applications containing citric acid and EDTA and Meade for teaching that sodium edetate and citric acid are known complexing agents.

Doi is generally directed to stabilizing an aqueous suspension of loteprednol etabonate and improving intranasal retention of the active ingredients. Doi is also concerned with the feeling-of-use using thickeners including cellulose derivatives such as methylcellulose, carboxymethylcellulose sodium, hydroxypropylmethylcellulose, etc., synthetic macromolecular compounds such as polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, etc., and saccharides such as sorbitol, mannitol, sucrose, etc.; cationic surfactants including quaternary ammonium salts; anionic surfactants including alkylsulfates; and nonionic surfactants including polysorbate 80, polyoxyethylene hydrogenated castor oil, etc.

Meade is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin

antagonists block endothelin. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

As discussed above, Flonase, Bernini, Harris, and Osbakken (alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. Appellants submit that the addition of Doi and/or Mead do not cure the noted deficiency of any combination of Flonase, Bernini, Harris, and Osbakken. More specifically, Flonase, Bernini, Harris, Osbakken, Doi, and Meade (considered alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. For at least this reason, claims 71-74 are not obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade.

3) Claims 75-76 are not obvious over any combination of Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over any combination Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

Claims 75-76 recite specific combinations of several active agents including fluticasone having the particular particle size distribution shown to beneficially exhibit unexpected results.

The Examiner cites Walker and Hamuy to propose that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are well-known anti-viral agents (Hamuy).

As discussed above, Flonase, Bernini, Harris, and Osbakken (alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. Appellants submit that the addition of Walker and/or Hamuy

do not cure the noted deficiency of any combination of Flonase, Bernini, Harris, and Osbakken. More specifically, Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy (considered alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. For at least these reasons, claims 75-76 are not obvious over any combination of combination Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

CONCLUSION

Appellants have shown that the Examiner has not met the requirements for establishing a *prima facie* case of obviousness under 35 U.S.C. §103(a) because the combination of the cited references fails to teach, suggest, or otherwise render predictable all aspects of the currently claimed invention. Additionally, one skilled in the art would have no rational basis for modifying the particle size distribution of Flonase in the manner proposed by the Examiner. Moreover, the currently claimed invention provides unexpected results as discussed in detail above. For at least these reasons, Appellants respectfully request that the Board overturn the rejections made by the Examiner and hold that the claims presently on appeal are in allowable form.

Respectfully submitted,

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8. ***Claims Appendix.***

1. A formulation for the treatment of fungus-induced rhinosinusitis in a mammal, said formulation comprising an aqueous suspension comprising:

(a) 0.04% to 0.06% by weight of suspended solid steroidal anti-inflammatory particles, wherein the steroidal anti-inflammatory is fluticasone or a pharmaceutically acceptable salt, ester, enol ether, enol ester, acid, or base thereof, said suspended solid steroidal anti-inflammatory having the following particle size distribution profile:

i. about 10% of the steroidal anti-inflammatory particles have a particle size of less than 0.4 microns;

ii. about 25% of the steroidal anti-inflammatory particles have a particle size of less than 0.8 microns;

iii. about 50% of the steroidal anti-inflammatory particles have a particle size of less than 1.5 microns;

iv. about 75% of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns; and

v. about 90% of the steroidal anti-inflammatory particles have a particle size of less than 5.3 microns; and

(b) an antifungal agent; wherein said formulation is suitable for administration to the nasal-paranasal mucosa.

4. The formulation of claim 1, wherein the antifungal agent comprises from 0.5 to 150mg of amphotericin β.

5. The formulation of claim 1, wherein said formulation comprises about 7.5 to about 15 mg of amphotericin β.

6. The formulation of claim 1, wherein said formulation comprises about 10 mg of amphotericin β.

10. The formulation of claim 1, comprising about 50 mcg of said steroidal anti-inflammatory.

11. The formulation of claim 1, comprising about 75 to about 300 mcg of said steroidal anti-inflammatory.

12. The formulation of claim 1, comprising 0.05% by weight of suspended solid fluticasone particles.

22. The formulation of claim 1, wherein the formulation is sterile.

23. The formulation of claim 1, wherein the formulation further comprises a preservative.

24. The formulation of claim 23, wherein the preservative is benzalkonium chloride.

25. The formulation of claim 1, wherein the formulation is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than 90% of the fluticasone originally present in the formulation still remains in the formulation.

27. The formulation of claim 1, wherein the formulation is in a metered-dose spray pump bottle.

28. The formulation of claim 1, further comprising about 0.01% to about 90% by weight on a dried weight basis of one or more of the following compounds:

(a) microcrystalline cellulose;

(b) carboxymethyl cellulose sodium;

(c) dextrose;

(d) benzalkonium chloride;

(e) polysorbate 80; and

(g) phenylethyl alcohol.

29. The formulation of claim 1, further comprising an antibiotic.

30. The formulation of claim 29, wherein the antibiotic is one or more selected from the group consisting of amikacin, azithromycin, aztreonan, cefazolin, cefepine, cefonicid, cefaperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cephapirin, ciprofloxacin, clindamycin, doxycycline, erythromycin lactobionate, gentamicin, kanamycin, linezolid, mezlocillin, mupirocin, nafcillin, netilmicin, neomycin, oxacillin, paromomycin, piperacillin, streptomycin, ticarcillin, tobramycin, and vancomycin.

35. A formulation for the treatment of fungus-induced rhinosinusitis, said formulation comprising an aqueous suspension comprising:

(a) about 7.5 to about 15 mg of amphotericin β.

(b) 0.04% to 0.06% by weight of suspended solid steroidal anti-inflammatory fluticasone propionate particles having the following particle size distribution profile:

ii. about 10% of the steroidal anti-inflammatory particles have a particle size of less than 0.40 microns;

iii. about 25% of the steroidal anti-inflammatory particles have a particle size of less than 0.80 microns;

iv. about 50% of the steroidal anti-inflammatory particles have a particle size of less than 1.5 microns;

v. about 75% of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns;

vi. about 90% of the steroid particles have a particle size of less than 5.3 microns; and,

wherein said formulation is suitable for administration to the nasal-paranasal mucosa.

71. The formulation of claim 1, further comprising at least at least one complexing agent selected from the group consisting of ethylenediaminetertraacetic acid, citric acid, nitrilotriacetic acid, salts thereof, and sodium edetate.

72. The formulation of claim 71, wherein the at least one complexing is sodium edetate.

73. The formulation of claim 35, further comprising at least at least one complexing agent selected from the group consisting of ethylenediaminetertraacetic acid, citric acid, nitrilotriacetic acid, salts thereof, and sodium edetate.

74. The formulation of claim 73, wherein the at least one complexing is sodium edetate.

75. A formulation for the treatment of fungus-induced rhinosinusitis, said formulation comprising an aqueous suspension comprising:

(a) a therapeutic amount of an antiviral agent selected from the group consisting of Acyclovir, Famciclovir, Valacyclovir, edoxudine, ganciclovir, foscarnet, cidofovir (vistide), Vitrasert and Formivirsen

(b) about 7.5 to about 15 mg of amphotericin β;

(c) about 10 to about 100 mg of doxycycline

(d) 0.04% to 0.06% by weight of suspended solid steroidal anti-inflammatory fluticasone propionate particles having the following particle size distribution profile:

ii. about 10% of the steroidal anti-inflammatory particles have a particle size of less than 0.4 microns;

iii. about 25% of the steroidal anti-inflammatory particles have a particle size of less than 0.8 microns;

iv. about 50% of the steroidal anti-inflammatory particles have a particle size of less than 1.5 microns;

v. about 75% of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns;

vi. about 90% of the steroid particles have a particle size of less than 5.3 microns; and,

wherein said formulation is suitable for administration to the nasal-paranasal mucosa.

76. The formulation of claim 75, wherein the antiviral agent is edoxudine.

77. The formulation of claim 35, wherein the formulation is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than 90% of the fluticasone originally present in the formulation still remains in the formulation.

9. ***Evidence Appendix.***

A. ChemImage

A copy of a White Paper titled "Comparison of Drug Particle Sizing of Innovator and Generic Nasal Spray Formulation Based on Raman Chemical Imaging" from ChemImage is provided herein. This paper was submitted for consideration on February 16, 2010. The Examiner entered this evidence as set forth in the Office Action dated March 3, 2010.

A. ChemImage

ChemImage™ White Paper

Comparison of Drug Particle Sizing of Innovator and Generic Nasal Spray Formulation Based on Raman Chemical Imaging

Two fluticasone propionate nasal spray formulations were characterized using Raman Chemical Imaging, for drug particle size distribution comparison between innovator and generic brands.

Measuring bioavailability (BA) and establishing bioequivalence (BE) for nasal aerosols and nasal sprays is required by U.S. Food and Drug Administration (FDA) for manufacturers in order to establish product quality in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) (1).

For nasal spray suspension formulations, bioequivalence studies should prove that the rate and the extent at which an active pharmaceutical ingredient (API) becomes available to active sites of the nasal cavity is within the acceptance criteria established for pharmaceutical equivalence of the innovator drug product. Drug particle size distribution (PSD) is a key parameter for establishing qualitative and quantitative sameness of these products in bioequivalence (BE) studies. Drug PSD correlates with formulation product quality criteria defined by the drug particle dissolution rate. The FDA recommends providing both drug and agglomerate PSD data in the BE submission (1). It is also recommended to evaluate the effect of the actuating device on deagglomeration by determining drug PSD and degree of drug particle agglomeration in the formulation pre- and post-actuation.

The FDA has recently initiated a document describing critical path opportunities for generic drug manufacturers (2). According to the office for generic drugs, if the drug PSD of test and reference products can be demonstrated to be equivalent, then *in vivo* biostudies may be waived for nasal spray suspensions. Today, optical microscopy is the only available technique to assess *in vitro* drug particle size distribution in sprays and aerosols to support BA or BE submission for NDAs and ANDAs. Even though a qualitative and semi-quantitative estimation of drug and aggregated drug PSD can be obtained based on microscopy analysis, visual microscopy is very subjective for positive identification of suspended drug substance in the presence of insoluble suspending agents. The occurrence of apparent drug particles due to insoluble excipients in the suspensions containing placebo products has led to false positive results (1). Reliable quantitative and qualitative methods for separately measuring the PSD of specific components and aggregates in the formulation are in demand by innovators and generic manufactures alike. Ingredient-specific particle sizing (ISPS) may be very valuable for formulation development, scale-up, batch release and batch comparison studies for innovator

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companies in the market of nasal sprays, while generic manufactures could use such information to support BE studies.

Wide-field chemical imaging technology combining optical microscopy and high throughput hyperspectral Raman Chemical Imaging (3) provides a unique opportunity to obtain ingredient-specific particle sizing of the drug in aqueous suspensions (4). This article features the application of Raman Chemical Imaging (RCI) technology for comparing the drug PSD of two nasal spray formulation samples containing a corticosteroid drug from brand and generic manufacturers.

Optical microscopy, Raman dispersive spectroscopy and RCI were used to study two commercially available fluticasone propionate aqueous nasal spray samples. All data were collected using a FALCON II™ Raman Chemical Imaging Microscope (ChemImage Corporation) with 532 nm laser excitation. Actuated samples were prepared by shaking, priming (four actuations each) and spraying each nasal spray sample in an upright position onto an inverted aluminum-coated glass microscope slide positioned approximately 15 cm from the spray nozzle. The samples were then immediately turned upright and allowed to dry.

Raman spectra of all individual components of the studied formulations are presented in Figure 1. RCI experiments were set up to spectrally discriminate the drug substance (fluticasone propionate) from all excipients. The discrimination of the analyte from other ingredients in the suspension is provided by the ability to collect spatially resolved Raman spectra in the image (pixel by pixel) and the ability to discriminate a characteristic Raman band of the drug (at 1663 cm-1) (5) from Raman bands of other materials in the spectral range. ChemImage Xpert™ software was used to acquire process and analyze RCI data for determining the ISPS distribution.

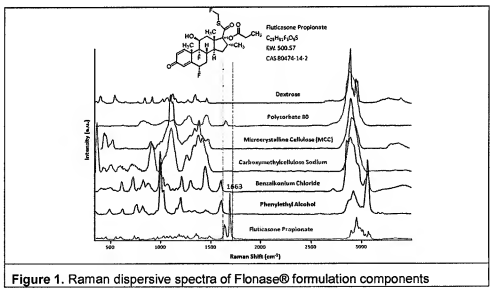


Figure 1. Raman dispersive spectra of Flonase® formulation components

Liquid Crystal Tunable Filter (LCTF) technology enables the collection of spectrally resolved imaging data in x and y dimensions of high resolution fidelity. RCI was performed on formulated generic and brand spray samples to obtain fluticasone-specific PSD for 100 particles per sample. In the current example, image contrast at the 1663 cm^{-1} Raman spectral plane can be attributed to the fluticasone propionate species (Figure 1). High intensity pixels at this wavelength are grouped with the close neighbors to spectrally define areas of the presence of fluticasone propionate within the image. A Raman Chemical Image of fluticasone propionate is superimposed or fused with an optical image of the same area to validate the binarization routine used for particle sizing. Figure 2a and 2b show representative brightfield reflectance images of both innovator and generic nasal sprays samples actuated onto a microscope slide. To achieve the desired count for drug particles per sample, a multiple field-of-view (FOV) montage was acquired. This montage is usually defined by the drug particle density approximated from a smaller subset of FOVs. A brightfield-guided image binarization (Figure 2, c, d) was then performed, and a particle size histogram for the drug substance was generated. Fusing both optical and RCI images is used to minimize the over- or underestimation of particle size compared to utilizing the RCI data alone and validate the accuracy of particle sizing.

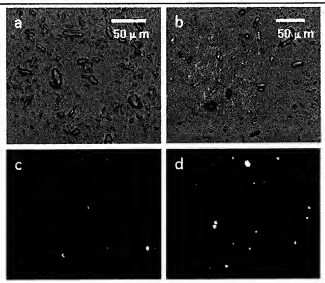
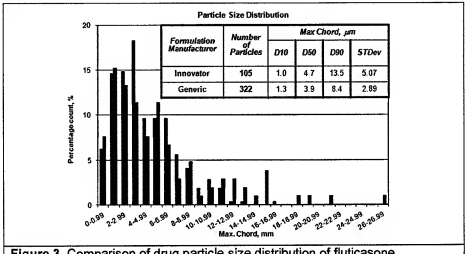


Figure 2. Representative brightfield reflectance image at 50x (a, b) and binarized chemical image of innovator (left) (c) and generic (right) (d) fluticasone propionate nasal spray samples



Formulation Manufacturer	Number of Particles	Max Chord, µm D10	D50	D90	STDev
Innovator	105	1.0	4.7	13.5	5.07
Generic	322	1.3	3.9	8.4	2.89

Figure 3. Comparison of drug particle size distribution of fluticasone propionate nasal spray samples for innovator and generic manufacturers

Comparison of these two products shows that the drug particle size distribution is similar (Figure 3) but the brand product possesses larger particles and a wider distribution of sizes. Figure 4a shows an example of brightfield/RCI fusion of the identified fluticasone propionate particles in the generic fluticasone propionate formulation. Aggregates and adhered particles can be detected and sized using such fusion strategies (Figure 4 b,c). While it is required by the FDA to report drug particle agglomeration, current analytical methods do not possess this capability. Moreover, without an ability to evaluate the presence and degree of drug-excipient agglomeration sizing by conventional optical microscopy is done on pre-selected particles by the analyst. Therefore, the drug PSD is likely to be subjective and differ from the true value when microscopy is used for drug particle sizing and reporting alone. There is a great interest to advance, validate and integrate ISPS algorithms for the automated analysis of drug PSD in final formulations(6), and Raman Chemical Imaging illustrates great promise for ISPS applications for nasal drug formulation manufacturers.

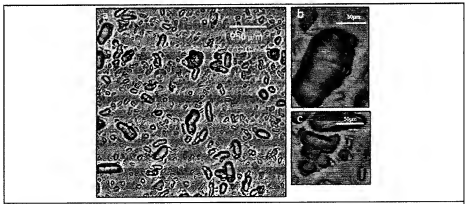


Figure 4. Brightfield reflectance image overlayed with pseudo-colored chemical image of generic fluticasone propionate nasal spray.

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10. ***Related Proceedings Appendix.***

There are currently no decisions by a court or the Board in a related proceeding.